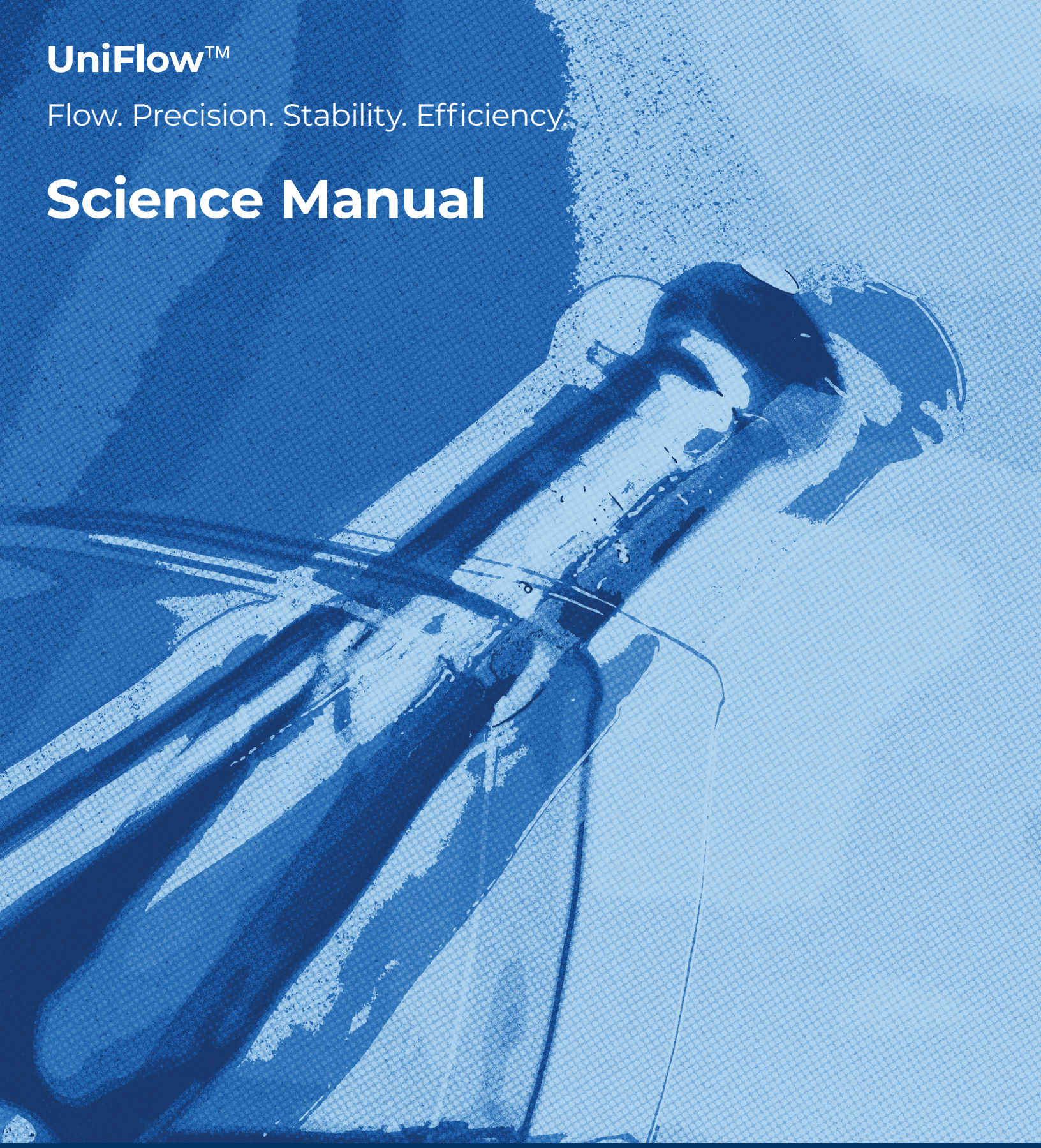
UniFlow™

Flow. Precision. Stability. Efficiency.

Science Manual



PCCA® SCIENCE

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Technical Reports

Characterization of the Physical Properties of the New Excipient Base Part 1: Scanning Electron Microscopy (SEM) Imaging

SUMMARY: Scanning Electron Microscopy (SEM) was used to compare the physical characteristics of two compounding excipients. PCCA UniFlow™ showed smoother, more uniform particles with less agglomeration. These features suggest improved flowability and content uniformity for compounding tablets and capsules.

Introduction:

When compounding solid dosage forms, such as tablets and capsules, the excipients used in the formulation play a pivotal role in enhancing flowability, compressibility and stability of the powder blend, ultimately ensuring uniformity of content in the final product. Understanding the physical characteristics of the excipients at a microscopic level provides crucial insights into their functionality during the compounding process.

Scanning Electron Microscopy (SEM) is a powerful tool used to visualize the surface morphology, size and shape, texture and agglomeration of materials, allowing compounding pharmacists to evaluate and compare excipient performance across different formulations.

The physical characteristics of the new excipient base, PCCA UniFlow™, were evaluated and compared to a commonly used compounding excipient: Microcrystalline Cellulose (MCC) NF (PH-105). The objective of this study was to identify potential differences that could influence flowability, compressibility and stability leading to potential differences in content uniformity.

Methodology:

The two excipients were provided by PCCA and the study was conducted by Particle Testing Authority (Norcross, GA). A portion of the powder from each sample was mounted on a carbon adhesive substrate and sputter-coated with gold for electrical continuity. The samples were imaged using a JEOL JSM-IT700HR field emission scanning electron microscope at increasing magnifications: 100x, 500x and 3,000x. Figure 1 illustrates the principle of SEM by showing the path of the electron beam and the key components involved in generating and detecting SEM images.

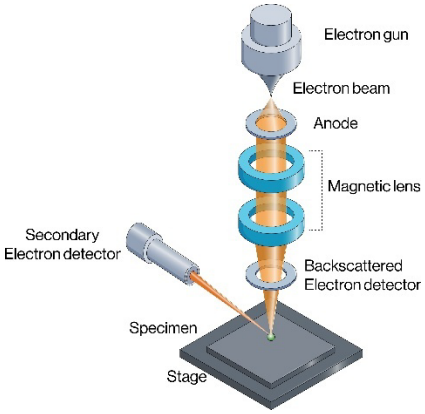


Figure 1. Scanning Electron Microscopy (SEM) instrumentation and principle diagram (*adapted from* Shutterstock illustration ID: 2491721153).

Results and Discussion:

High-resolution, grayscale SEM images were taken for the two excipients at increasing magnifications (100x, 500x and 3,000x), as shown in Figure 2. Samples were compared according to three different parameters: surface morphology; size and shape; texture and agglomeration (Table 1).

MCC NF (PH-105) is a purified, partially depolymerized form of cellulose that exhibits a distinct morphology of fibrous or rod-like particles. As observed in Figure 2, elongated and angular particles dominate, and there is visible agglomeration likely due to interlocking shapes. At high magnifications, the texture appears porous or rough.

In contrast, PCCA UniFlow shows relatively uniform particles with smoother surfaces, and a moderate surface texture, not highly porous. There is limited agglomeration as particles are more discrete and less clumped. As such, the new excipient base is expected to provide superior flowability and content uniformity, making it an ideal excipient for compounding solid dosage forms (Table 1).

Characterization of the Physical Properties of the New Excipient Base Part 1: Scanning Electron Microscopy (SEM) Imaging

Table 1. Comparison of the physical characteristics of PCCA UniFlow and MCC NF (PH-105) according to morphology, size and shape, texture and agglomeration; and predicted implications on the flowability and content uniformity of the powder samples.

Powder Samples	Morphology	Size and Shape	Texture and Agglomeration	Flowability and Content Uniformity
PCCA UniFlow	Predominantly rounded, uniform particles	Consistent, moderately-sized particles	Smooth particles, low agglomeration	Superior (*predicted*)
Microcrystalline Cellulose NF (PH-105)	Predominantly fibrous, irregular particles	Inconsistent and broad size range	Rough/porous particles, moderate agglomeration	Inferior (*predicted*)

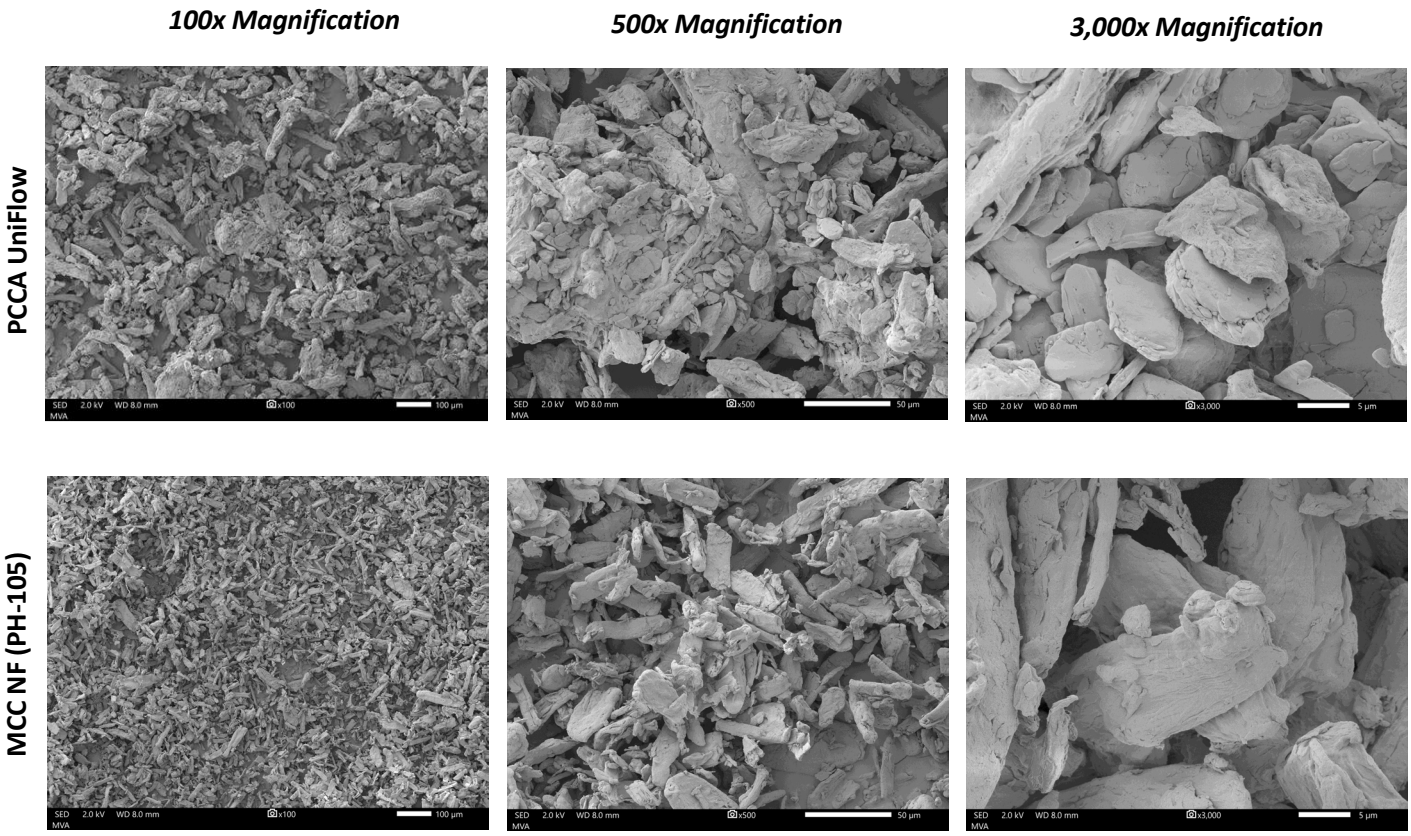


Figure 2. Powder samples for PCCA UniFlow and MCC NF (PH-105) imaged using a field emission scanning electron microscope at increasing magnifications (100x, 500x and 3,000x).

Characterization of the Physical Properties of the New Excipient Base Part 2: Powder Flowability

SUMMARY: Powder flowability is an important physical characteristic that influences the quality of powder mixtures and the efficiency of mixing processes. PCCA UniFlow™ was evaluated and compared to the commonly used compounding excipient MCC NF (PH-105), and it was concluded that the new excipient base demonstrates significantly superior flowability, based on the testing of six powder characteristics: angle of repose, aerated and packed bulk density, compressibility, angle of spatula and cohesion/uniformity.

Introduction:

Flowability is an important physical property of powders that influences the ability to achieve consistent and homogeneous mixtures. It refers to a powder's ability to flow smoothly and predictably, which directly impacts the quality and efficiency of mixing processes. Poor flowability can lead to uneven mixing, blockages in equipment, and difficulties in handling and packaging, ultimately affecting the integrity of the final product. The powder flowability of the new excipient base, PCCA UniFlow™, was evaluated and compared to a commonly used compounding excipient: Microcrystalline Cellulose (MCC) NF (PH-105).

Methodology:

The Hosokawa Powder Tester PT-X (Figure 1) was used to measure powder flowability. The PT-X employs the methods developed by Ralph L. Carr (Carr Indices) to determine the flowability of dry powders. In this study, six powder characteristics were analyzed: angle of repose, aerated bulk density, packed bulk density, compressibility, angle of spatula and cohesion/ uniformity. These tests assess how powders behave when transitioning from static to dynamic states. The measured values are assigned to indices on the standardized analysis of about 3,000 different bulk materials by R.L. Carr.

The two excipients, PCCA UniFlow and MCC NF (PH-105), were provided by PCCA and the study was conducted by Measurlabs (Helsinki, Finland). Before testing, samples were homogenized by rotating the containers to ensure representativeness. Approximately 300 mL of powder was used per test, which was conducted at 23–24°C and 45–48% relative humidity. Each sample was tested in duplicate, with results averaged.

Figure 1. Powder Tester PT-X (*adapted from* Hosokawa Micron B.V., 2025).

Results and Discussion:

PCCA UniFlow displayed lower angle of repose, lower compressibility and lower angle of spatula, as shown in Table 1.

The angle of repose is measured by subjecting the standard sieve (710 µm) to vibration and letting the sample pass through a funnel on a horizontal plate, forming a heap whose angle is recorded; lower angles indicate better flowability. Compressibility is the value which has the greatest effect on flowability of a powder. It is obtained by taking the ratio of the aerated bulk density (freely settled) and the packed bulk density (after tapping); higher compressibility is associated with poor flowability.

The angle of the spatula reflects a material's internal friction and is measured by the angle formed by the powder that builds up on the spatula. The greater this characteristic, the poorer the powder's flowability. Cohesion is measured by vibrating a standard sieve for a set time and force, then seeing how much powder passes through.

Characterization of the Physical Properties of the New Excipient Base Part 2: Powder Flowability

The cohesion test was not conducted on PCCA UniFlow as the particle size uniformity test was deemed more appropriate. Uniformity is quantified as the ratio of the particle diameters at the 60th percentile (d60) to those at the 10th percentile (d10) within the particle size distribution of the sample.

The measured values of the six powder characteristics were used to calculate the Carr Index of Flowability. PCCA UniFlow displayed an index of 65.5, whereas MCC NF (PH-105) displayed an index of 46 (Table 1). The classification of the flowability index according to Carr states that an index of 40–59 is poor, whereas 60–69 is passable (Table 2). Despite the visual similarity between the two samples, MCC NF (PH-105) scored much lower on flowability, more specifically on compressibility. During testing of MCC NF (PH-105), static effects made the powder stick to the chutes in the angle of spatula and compressibility tests. This may have also affected the particle settling behavior during the aerated density test, resulting in higher compressibility.

In conclusion, PCCA UniFlow demonstrates significantly superior flowability compared to MCC NF (PH-105), indicating that the new excipient base may enable higher-quality powder mixtures and more efficient mixing processes.

Table 2. Classification of the flowability index according to Carr.

Carr Index	Flowability	Performance
90-100	Excellent	Aid is not needed, will not arch
80-89	Good	Aid is not needed, will not arch
70-79	Fair	Aid is not needed but vibration is sometimes required
60-69	Passable	Borderline; material may hang up
40-59	Poor	Agitation or vibration is needed
20-39	Very Poor	Agitate more positively
0-19	Very Very Poor	Special agitation, hopper or engineering

Table 1. Comparison of powder characteristics and Carr Index of PCCA UniFlow and MCC NF (PH-105).

Powder Samples	Angle of repose (deg.)	Aerated bulk density (g/cm³)	Packed bulk density (g/cm³)	Compressibility (%)	Angle of spatula (deg.)	Cohesion / Uniformity	Carr Index
PCCA UniFlow	44.8	0.443	0.631	29.9	54.2	5.2	**65.5**
Microcrystalline Cellulose NF (PH-105)	45.1	0.254	0.517	50.9	56.4	3.7	**46**

Uniformity Testing of Powder Triturates for T3/T4 Mixed with the New Excipient Base Using Variable Methods: Mortar and Pestle, FlackTek™ and PCCA RAM™

SUMMARY: Uniformity of APIs is essential for therapeutic efficacy and patient safety. In this study, powder triturates for T3 and T4 were prepared using three mixing methods for comparison purposes and were tested for content uniformity (adapted). The powder triturates demonstrated potency within the 90-100% specification, with uniform distribution of T3 and T4 across all mixing methods, highlighting the role of the new excipient base in enhancing flow, mixing efficiency and overall formulation quality for accurate dosing.

Introduction:

Uniformity of dosage units is critically important to ensure that each individual unit (e.g., tablet, capsule) in a batch contains the intended amount of active pharmaceutical ingredient (API), within a narrow range around the label claim (90-110% specification). This guarantees both the therapeutic efficacy of the treatment and the safety of the patient by minimizing the risk of underdosing or overdosing. When preparing solid dosage forms, the powder characteristics may affect uniformity due to poor flowability, segregation or inconsistent mixing techniques.

In this study, the uniformity of powder triturates was tested to confirm the quality of the mixture prior to preparing the individual dosage units. Three mixing methods were used for comparison purposes: Mortar and Pestle (M&P), FlackTek™ and PCCA RAM™ (Fig. 1).

Figure 1. PCCA RAM™: ResonantAcoustic® Mixer.

The APIs chosen for this study were liothyronine sodium (T3) and levothyroxine sodium (T4) due to the sensitive dose-response relationship and serious consequences with small dose variations. T4 is recognized as a Narrow Therapeutic Index (NTI) drug by the FDA. The powder triturates for T3 and T4 were prepared at 1:1000 (0.1%) dilution. The corresponding PCCA formulas are as follows:

- 15642 Levothyroxine Sodium (T4) 1:1000 (0.1%)
- 15643 Levothyroxine Sodium (T4) 1:1000 (0.1%)
- 15644 Levothyroxine Sodium (T4) 1:1000 (0.1%)
- 15646 Liothyronine Sodium (T3) 1:1000 (0.1%)
- 15647 Liothyronine Sodium (T3) 1:1000 (0.1%)
- 15648 Liothyronine Sodium (T3) 1:1000 (0.1%)

UniFlow Triturations (PCCA RAM™)

Methodology:

As outlined in USP Chapter ⟨905⟩ Uniformity of Dosage Units, *Content Uniformity* is one of the two methods to demonstrate the uniformity of dosage units. When applicable to solid dosage forms, it requires individually assaying 10 units using an appropriate analytical method. For the purposes of assaying the powder triturates for T3/T4, the content uniformity method was adapted to assume that each sample drawn from the mixture corresponded to a single dose. A total of 10 samples were collected for both the T3 and T4 powder triturates. The APIs were extracted using 80% ethanol in purified water through a combination of vortex-mixing, sonication and centrifugation before transferring to HPLC vials for analysis. Standard solutions were prepared to achieve a known concentration of about 0.4 mg/mL stock, then diluted to various concentrations. The mobile phases consisted of 0.1% trifluoroacetic acid (TFA) in water (Mobile Phase A) and 0.1% TFA in acetonitrile (Mobile Phase B). Chromatographic analysis was conducted using a Waters Acquity UPLC system with reverse-phase gradient elution and a detection wavelength of 300 nm over a 2.5-minute run time. The product uniformity could be evaluated by RSD% value, which should be kept as low as possible. An RSD <5% would ensure the uniformity of the final product.

Uniformity Testing of Powder Triturates for T3/T4 Mixed with the New Excipient Base Using Variable Methods: Mortar and Pestle, FlackTek™ and PCCA RAM™

Results and Discussion:

Potency refers to the amount of API present in a drug product compared to its label claim. For compounded preparations, USP standards dictate that the amount of API must be ±10% of the label claim, unless the monograph of the preparation states otherwise. As such, the powder triturates for T3/T4 should have potency between 90% and 110%. However, the USP monograph for the T4 capsules dictates a potency between 95% and 105%. If the corresponding powder triturates for T4 test outside this range, an adjustment must be made when preparing the capsules to meet the specifications. The potency, average, standard deviation (SD), relative standard deviation (RSD) and difference for the 10 samples of T3 and T4 powder triturates are displayed in Tables 1 and 2, respectively.

Conclusion:

It is concluded that the potency for both powder triturates was within the specifications of 90% and 110%, with acceptable standard deviations below 5.

T3 and T4 were found to be consistently distributed across the test samples, confirming the uniformity of the corresponding powder triturates regardless of the mixing method (M&P, FlackTek™ and PCCA RAM™). This consistent distribution highlights the performance of the new excipient base in enhancing flow properties and mixing efficiency, thereby minimizing the risk of segregation during compounding. These attributes contribute significantly to the overall quality, reliability and reproducibility of the powder triturates, supporting accurate and consistent dosing of T3 and T4.

Tables 1 and 2. Potency (%) of 10 samples of T3 and T4 powder triturates, respectively, obtained using the three mixing methods; average, SD and difference are displayed in the corresponding annexed tables.

Sample	M&P	FlackTek™	PCCA RAM™
1	103.980	96.978	98.207
2	103.406	97.404	101.257
3	102.205	98.576	95.834
4	101.518	102.144	95.191
5	100.847	100.578	100.676
6	101.979	98.322	97.625
7	102.470	99.337	95.698
8	103.894	96.295	95.476
9	101.114	96.785	96.046
10	101.229	99.833	97.490
Average	102.264	98.625	97.350
SD	1.351	1.927	2.213
RSD	1.321	1.954	2.273
Difference	3.133	5.849	6.066

Sample	M&P	FlackTek™	PCCA RAM™
1	98.231	94.375	98.255
2	100.513	95.510	102.623
3	99.586	99.413	102.697
4	99.661	96.480	98.247
5	101.740	98.012	99.760
6	100.003	96.921	100.787
7	100.282	97.968	98.179
8	101.350	96.834	97.567
9	100.995	96.369	102.842
10	97.947	98.060	101.206
Average	100.031	96.994	100.216
SD	1.464	1.592	2.204
RSD	1.464	1.641	2.199
Difference	3.793	5.038	5.275

Dissolution Profile of T3 and T4 Capsules Compounded with the New Excipient Base and Also with Microcrystalline Cellulose (MCC)

SUMMARY: Dissolution testing of T3 and T4 capsules compounded with the new excipient base (PCCA UniFlow™) was conducted to evaluate their release profile, in comparison to formulations prepared with MCC. The results obtained demonstrate rapid and high cumulative release for both drugs, thus confirming that the new excipient base successfully supports the release of T3 and T4 from solid dosage forms.

Introduction:

Dissolution is a key quality control parameter for assessing the release profile of active pharmaceutical ingredients (APIs) from solid dosage forms, as it directly influences both the rate and extent of drug absorption in the body.

Levothyroxine sodium (T4) 100 micrograms and liothyronine sodium (T3) 25 micrograms capsules (size 1) were compounded using the new excipient base, PCCA UniFlow™, and also microcrystalline cellulose (MCC) for comparison purposes.

Methodology:

Dissolution testing was performed in accordance with USP General Chapter ⟨711⟩ Dissolution, using a modified USP Apparatus 2 (Paddle) with a 100 mL volume vessel, instead of the standard 500–1000 mL, to allow detection of the low amount of APIs released from the tablets. Testing was performed in pH 10.0 ± 0.05 alkaline borate buffer medium, using the Paddle Apparatus at 50 rpm (revolutions per minute) with sampling at 0, 15, 30, 45 and 60 minutes.

Standard stock solutions of T3 and T4 0.1 mg/mL in 80% ethanol were prepared and diluted with medium to obtain calibration ranges of 0.125–0.375 µg/mL for T3, and 0.5–1.5 µg/mL for T4. Sample solutions were filtered through 0.2 µm PVDF membranes, with the dissolution medium replenished after each withdrawal.

Assay quantification was performed on a Waters Acquity UPLC system equipped with a BEH C_{18} column (2.1 × 50 mm, 1.7 µm). Reverse-phase gradient elution was carried out using mobile phase A (0.1% TFA in water) and mobile phase B (0.1% TFA in acetonitrile). Detection was set at 240 nm, with a column temperature of 65°C, a flow rate of 0.7 mL/min and a total run time of 2.5 minutes.

Results and Discussion:

The dissolution profile for T3 in PCCA UniFlow shows a rapid release reaching approximately 85–90% within 20 min, plateauing thereafter (Fig. 1). The release of T4 approached about 90% within 30 min, also stabilizing afterwards (Fig. 2). The dissolution of T3/T4 in MCC showed similar profiles to the new excipient base, which is desired to maintain consistency with established release characteristics to which patients are physiologically adapted.

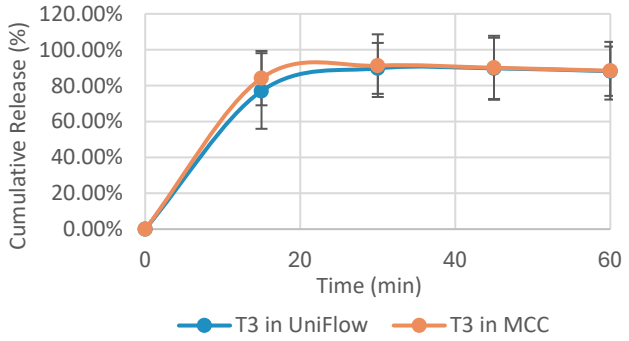


Figure 1. Dissolution profile for T3 in UniFlow versus MCC.

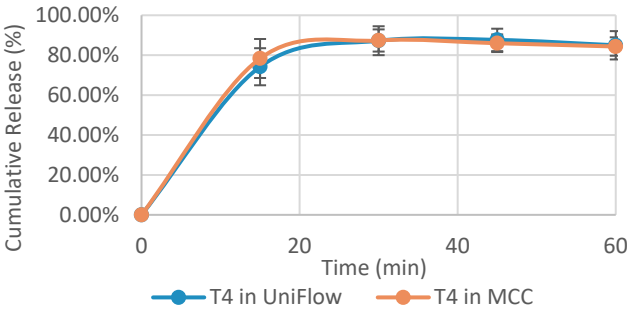


Figure 2. Dissolution profile for T4 in UniFlow versus MCC.

Dissolution testing may be used as a predictor of *in vivo* drug performance by providing insights into the rate and extent of APIs release from the dosage forms. T3 and T4 were successfully released from the capsules compounded with the new excipient base, supporting its suitability for formulation development in pharmaceutical compounding.

Chemical Stability of Powder Triturates for T3/T4 Mixed with the New Excipient Base Using Variable Methods: Mortar and Pestle, FlackTek™ and PCCA RAM™

SUMMARY: Powder triturates for T3/T4 mixed with PCCA UniFlow™ remained chemically stable for 6 months at room temperature and refrigerated conditions, regardless of the mixing method: M&P, FlackTek™ or PCCA RAM™.

Introduction:

Thyroid hormones (liothyronine T3 and levothyroxine T4) are potent and low-dose active pharmaceutical ingredients (APIs), often measured in micrograms (µg) per dosing unit. As such, even slight chemical degradation can lead to clinically significant under- or overdosing, risking hypo- or hyperthyroidism. Compatibility with the new excipient base (PCCA UniFlow™) must be ensured when compounding solid dosage forms (tablets and capsules) to guarantee that there is no chemical interaction responsible for degradation of the APIs.

The chemical stability of powder triturates for T3/T4 mixed with the new excipient base and stored at room temperature and refrigerated conditions was evaluated. The powder triturates were prepared using three different methods for comparison purposes: mortar & pestle (M&P), FlackTek™ and PCCA RAM™.

Methodology:

T3 and T4 were extracted using 80% ethanol in purified water through a combination of vortex-mixing, sonication and centrifugation before transferring to HPLC vials for analysis. Standard solutions were prepared to achieve a known concentration of about 0.4 mg/mL stock, then diluted to various concentrations. The mobile phases consisted of 0.1% trifluoroacetic acid (TFA) in water (Mobile Phase A) and 0.1% TFA in acetonitrile (Mobile Phase B). Chromatographic analysis was conducted using a Waters Acquity UPLC system with reverse-phase gradient elution and a detection wavelength of 300 nm over a 2.5-minute run time. Assay determination was performed using a Waters separation module (QSM), a Waters column manager heater/cooler (CM), a Waters Acquity photodiode array (PDA) detector and a Waters auto sampler (FTN).

Results and Discussion:

The potency of the T3/T4 powder triturates remained within the specifications of +/-10% of the initial concentrations, as displayed in Tables and Figures 1, 2 (A, B).

The new excipient base (PCCA UniFlow) maintained the chemical stability of the T3/T4 powder triturates over 6 months, when stored at both room temperature and refrigerated conditions. The three mixing methods tested — M&P, FlackTek and PCCA RAM — yielded comparable results, supporting the suitability of PCCA UniFlow when compounding T3/T4 solid dosage forms, regardless of the compounding equipment used.

A

Day	M&P	FlackTek™	PCCA RAM™
0	100.00%	100.00%	100.00%
27-29	99.97%	98.72%	94.31%
59	98.70%	97.01%	97.18%
91	96.96%	95.94%	95.69%
120	98.15%	96.72%	95.80%
150	99.46%	97.96%	95.48%
182	97.20%	96.37%	95.41%

B

Day	M&P	FlackTek™	PCCA RAM™
0	100.00%	100.00%	100.00%
27-29	100.50%	98.74%	98.69%
59	99.09%	97.92%	97.18%
91	97.26%	97.64%	96.47%
120	98.87%	98.61%	96.47%
150	99.52%	99.37%	97.78%
182	97.66%	97.22%	95.77%

Tables 1A and 1B. Potency (% initial) of **T4** powder triturates obtained using the three mixing methods, stored for 6 months at room temperature (A) and refrigerated conditions (B).

Please refer to page 2 for additional Tables and Figures.

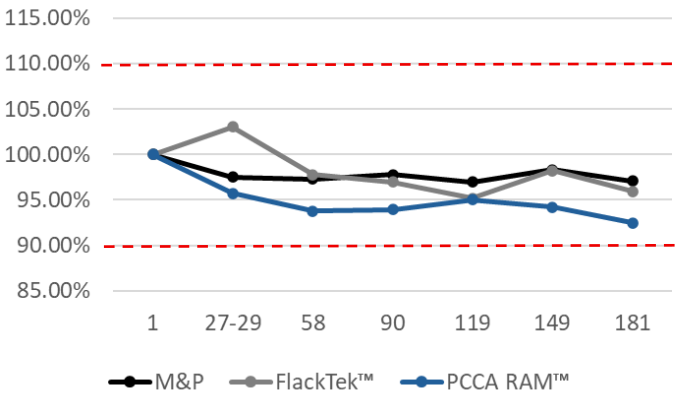
Chemical Stability of Powder Triturates for T3/T4 Mixed with the New Excipient Base Using Variable Methods: Mortar and Pestle, FlackTek™ and PCCA RAM™

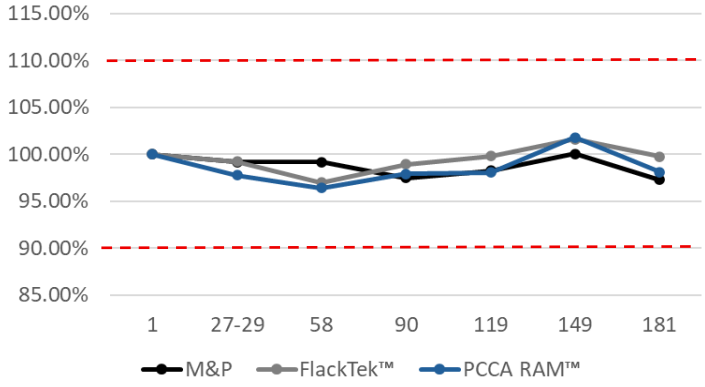
A

Day	M&P	FlackTek™	PCCA RAM™
1	100.00%	100.00%	100.00%
27-29	97.52%	103.05%	95.72%
58	97.30%	97.77%	93.77%
90	97.81%	96.96%	93.95%
119	96.96%	95.21%	95.03%
149	98.33%	98.23%	94.24%
181	97.07%	95.97%	92.49%

B

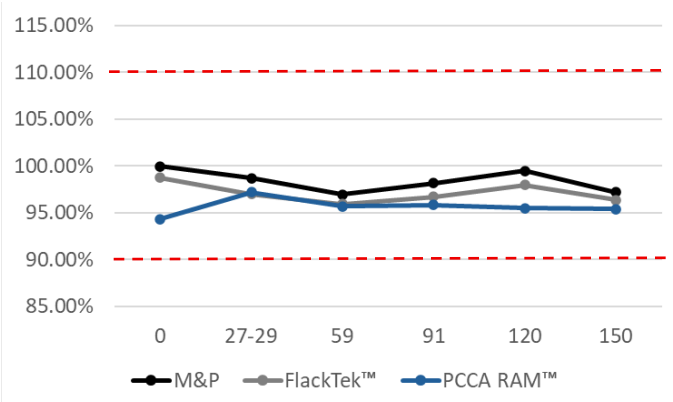
Day	M&P	FlackTek™	PCCA RAM™
1	100.00%	100.00%	100.00%
27-29	99.19%	99.26%	97.76%
58	99.17%	97.01%	96.41%
90	97.49%	98.93%	97.94%
119	98.28%	99.83%	98.06%
149	100.07%	101.61%	101.83%
181	97.30%	99.75%	98.10%



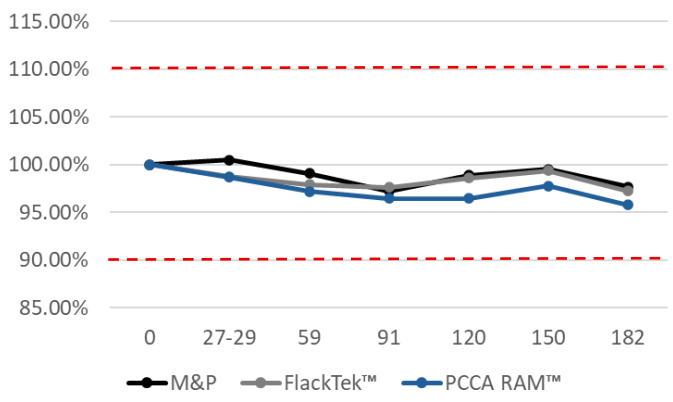


Tables and Figures 2A and 2B. Potency (% initial) of **T3** powder triturates obtained using the three mixing methods, stored for 6 months at room temperature (A) and refrigerated conditions (B).

A



B



Figures 1A and 1B. Potency (% initial) of **T4** powder triturates obtained using the three mixing methods, stored for 6 months at room temperature (A) and refrigerated conditions (B).

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